REMARKS

Claim 21 has been amended as kindly suggested by the Examiner. Claim 22 has been amended to clarify that different glycoprotein hormones are referred to, such that if one β subunit is derived from LH, the other must be derived from CG, FSH or TSH. As these amendments are solely for clarification, no new matter has been added and entry of the amendment is respectfully requested.

The title has been changed to be more descriptive. Applicants realize that this is not a complete description of what is being claimed, but it is assumed that the title needs to be of reasonable length. If the Office would prefer another title, applicants are open to suggestions for a succinct title that would provide sufficient clarity.

The invention is directed to isolated compositions wherein a β subunit of a glycoprotein hormone is coupled covalently optionally through a linker, to the α subunit common to the glycoprotein hormones, and non-covalently to another β subunit associated with glycoprotein hormones. The proviso in claim 1 is provided to exclude a composition obtained in un-isolated form by the inventors and disclosed in an abstract. The various bases for rejection are addressed below.

The Claim Objections

Claim 21 was objected to because it is said to encompass non-elected inventions wherein there is a covalent linkage. Applicants do not understand this objection as the claim as originally elected was directed to compositions that contain a covalent linkage between β^1 and α and a non-covalent linkage of this single-chain form to an additional β^2. It is not clear to applicants how the Office wishes this claim to be pared.

Claims 21-23, 25 and 27-28 were objected to for encompassing non-elected species. These claims have been left in their original form since applicants believe that generic claim 21 will be found allowable, permitting non-elected species to be included in the dependent claims. If applicants have misunderstood this objection, a telephone call to the undersigned representative would be appreciated.

The Rejection Under 35 U.S.C. § 112, Paragraph Two

All claims were rejected under this section of the statute, although only claims 21 and 22 appear to be the basis, the remaining claims being rejected for being dependent thereon.

As to claim 21, applicants believe the claim is readily interpretable. It will be noted that in both cases β^1 is covalently coupled to the α subunit and β^2 is non-covalently coupled to the single-chain form. The formulas (1) and (2) are complementary only in the sense that the single-chain form in formula (1) has the α subunit at the N-terminus and formula (2) has the α subunit at the C-terminus of the single-chain forms. In both cases, it is only β^1 that is covalently linked, optionally through a linker, to an α subunit. Therefore, the proviso excludes only the case wherein the covalently linked subunit is CG and the non-covalently linked subunit is FSH. So, claim 21 states that if the covalently linked β subunit is CG, then the non-covalently linked subunit cannot be FSH.

The wording of claim 22 has been revised to clarify that it refers to β subunits of different isoprotein hormones are variants of these subunits. It is believed that the amendment to claim 22 disposes of the rejection.

Double-Patenting

All claims were rejected as obviousness-type double-patenting over claims 25-30 of U.S. patent 6,635,256. A terminal disclaimer with respect to this patent is enclosed, thus disposing of this rejection.

The Rejection Under 35 U.S.C. § 102

Claims 21-23 and 25 were rejected as assertedly anticipated by Sugihara, *et al., PNAS* (1995) 92:2041-2045.

Applicants appreciate the suggestion made by the Examiner that requiring that the claimed composition be "isolated" would overcome this rejection. This has been done, and thus the rejection may be withdrawn.

The Rejection Under 35 U.S.C. § 103

Claims 21-23 and 28 were rejected under this section as assertedly obvious over De Rosa, *et al., Annales d'Endocrinologie* (1987) 48:468-472 (Abstract only) in view of Hyde, *et al., Biol. of Reproduction*, Abstract 193 (1996) and Ben-Menahem, *et al.,* Abstract OR28-3, Endocrine Society (1998).

First, applicants note with appreciation that claims 25 and 27 are not included in this rejection.

De Rosa is cited, it is assumed, to show that it is known in the art to administer more than one glycoprotein hormone activity to humans. Hyde is said to teach that co-administration of hCGβα and FSH β results in activities of both hormones and that Ben-Menahem to teach that co-administration of FSHβα and hCGβ results in both activities. According to the Office, it would be obvious to substitute these constructions for the individual hormones utilized by De Rosa.

The characterization of Hyde and Ben-Menahem is not exactly correct. First, neither abstract teaches co-administration to any subject. In each case, supernatants from CHO cells that express separate constructs, one encoding a single-chain glycoprotein and the other encoding a β subunit of a different glycoprotein, were tested only for receptor binding activity and adenylate cyclase activity. This would be an *in vitro* experiment.

Second, both abstracts indicate that the *in vitro* tests were designed to determine whether the complexes presumably formed in the CHO cells were responsible for the activity of both hormones. In each case, the authors concluded that no such conclusion could be drawn because the complex had not been isolated. Therefore, the authors state that it was fair to draw the conclusion that the activity of the β subunit that was independently generated must have been exhibited by virtue of its association with the single-chain form (since the β subunit is not effective absent association with an α subunit). However, it was not shown that the β subunit covalently bound to α was active when in the complex constructed as set forth in the present claims. It could still be the case that the single-chain form, independent of the associated, non-covalently bonded, second β subunit, was responsible for this activity.

The invention requires a non-covalent linkage between the β^2 subunit and the single-chain glycoprotein containing β^1 and α. It further requires that these compositions be isolated. Neither Hyde nor Ben-Menahem describe these isolated complexes or demonstrate that the activities of both subunits are retained in such a complex.

In addition, it should be noted that the complex form in Hyde, although not isolated, is explicitly excluded from the claims – *i.e.*, the complex in which the CG is covalently bound to α

(β^1) and FSH is non-covalently associated with the single-chain hormone (β^2). Thus, the complex formed in the Hyde abstract is not even included in the invention.

With respect to Ben-Menahem, this abstract is the work of the present inventors published within one year of the present application. Enclosed is a Declaration of Dr. Irving Boime attesting to the fact that the co-authors of the abstract (other than David Ben-Menahem), worked entirely under his and Dr. Ben-Menahem's direction and did not contribute to the concept of the invention. As there is no presumption, even, that co-authors of a publication made inventive contributions (*In re Katz*, 687 F2d 450, 215 USPQ 14 (CCPA 1982)), it is believed that Ben-Menahem can be withdrawn as a citation. Since the rejection depends on the combination of all three documents, removal of one of these documents from consideration should automatically cause the rejection to be withdrawn. The rejection may also be withdrawn on other grounds as noted above.

In summary, De Rosa merely teaches that it is sometimes desirable to administer more than one glycoprotein hormone to humans. There is no suggestion in De Rosa that this might be done using the complexes of the invention. Neither Hyde nor Ben-Menahem teach that the complexes of the invention can be used to confer the activity of both glycoproteins whose β subunits are included. Both teach that although it has been established that such complexes can be formed, it cannot be concluded that both activities are exhibited by the complex itself. Further, the complex of Hyde is not included in the invention and Ben-Menahem is removed as a citable document as it is the work of the inventors themselves within one year of application.

For this reason, the rejection of claims 21-23 and 28 may be withdrawn.

Summary

Claim 21 has been amended as suggested by the Examiner to overcome the rejection for anticipation. It has been explained that the claim is clear as presently proposed. Claim 22 has been amended to overcome the rejection for indefiniteness. The double-patenting rejection has been mooted by the submission of a terminal disclaimer. Only claims 21-23 and 28 were rejected as obvious, so it is clear that claims 25 and 27 are allowable (claim 27 appears not to have been rejected on any basis other than double-patenting). In view of the discussion above, it is believed that the obviousness rejection of claims 21-23 and 28 can be withdrawn and passage of all pending claims, claims 21-28, to issue is respectfully requested. The allowability of the examined claims would permit the restoration of the withdrawn claims 24 and 26 since claim 21 is a linking claim.

Should any issues remain that might be resolved by a telephone conversation, a call to the undersigned would be appreciated.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 295002005901.

Respectfully submitted,

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